Central nervous control of metabolism

Scheurink, Antonius Johannes Willibrordus

SUMMARY

Maintenance of the availability of the predominant energy substrates glucose and free fatty acids (FFA) is crucial for survival of the organism. Hormonal and neural regulatory factors form the basis for sensitive and very specific mechanisms regulating energy metabolism. Hormonal factors include catecholamines from the adrenal medulla and insulin and glucagon from the endocrine pancreas. With regard to the neural regulatory factors, both the sympathetic and parasympathetic nervous system, as well as neuroendocrine responses from the hypothalamus-pituitary axis may be involved. Under basal metabolic conditions peripheral glucose and FFA concentrations are principally controlled by hormonal regulatory factors. The role of the central nervous system in the regulation of peripheral energy metabolism becomes gradually more important under nonbasal conditions like for example exercise.

The hypothalamus is regarded as an important integrative station in the central nervous control of peripheral blood glucose and FFA metabolism. More in detail, particularly catecholamine sensitive neurons in the ventromedial (VMH), the lateral (LHA), and the paraventricular (PVN) hypothalamic areas seem to play a role.

In the first part of this thesis the involvement of the hypothalamic catecholamine sensitive neurons in the regulation of peripheral glucose and FFA concentrations during exercise was investigated in rats. Exercise consisted of either treadmill running at a speed of 26 m/min for 20 min, or strenuous swimming against a counter current (13 m/min) for 15 min in a pool with water of 33°C. The normal functioning of the hypothalamus was suspended by intrahypothalamic infusion of long-acting neural antagonists. Metabolic and hormonal responses were followed in blood samples frequently taken before, during, and after hypothalamic infusion and exercise.

Anesthesia of the VMH and infusion of adrenoceptor antagonists into the VMH, the LHA, and the PVN markedly reduced the exercise-induced increase in hepatic glucose production and, as a consequence, in blood glucose concentrations. Blockade of β-adrenoceptors in the VMH and LHA markedly reduced the exercise-induced increase in plasma FFA concentrations.

The results suggest that a general wide spread hypothalamic mechanism, including both α- and β-adrenoceptors in PVN, VMH, as well as LHA, is essentially involved in the central nervous regulation of blood glucose levels during exercise. Furthermore, the data point to a β-adrenoceptor mediated plasma FFA regulating mechanism, located in the ventral and somewhat medial area of the hypothalamus. It may be argued that in the present experiments actually those areas in the hypothalamus were identified that integrate the information regarding substrate levels in the general circulation with the initially nondiscriminating "central command" in response to exercise. The central noradrenergic pathways, arising in the A1 and A2 cell groups in the brain stem and projecting to the hypothalamus through the ventral noradrenergic bundle, are probably involved in the transmission of signals concerning peripheral glucose and FFA concentrations to the glucose and FFA regulating regions in the hypothalamus. The hypothalamus can thus be considered as one of the major levels of organization in the brain coordinating the autonomic output in response to exercise.

The pathways by which the catecholamine sensitive neurons within the hypothalamus exert their regulatory function on peripheral glucose and FFA metabolism during exercise were hitherto unknown. Activation of the sympathoadrenal system leading to increased plasma levels of epinephrine (E) and norepinephrine (NE) seemed to be involved. In the present study, anesthesia of the VMH in running rats caused a reduction in the exercise-induced increase in the plasma levels of E and NE. Blockade of LHA α-adrenoceptors enhanced the normal increase in NE concentrations during exercise. The increase in plasma NE was reduced after β-adrenoceptor blockade in the VMH and PVN. The exercise-induced increase in plasma E was reduced after α-adrenoceptor blockade in the VMH, whereas β-adrenoceptor blockade in the VMH and LHA had the opposite effect. The changes in sympathoadrenal activity induced by hypothalamic adrenoceptor blockade and exercise were, however, not in accordance with the alterations in blood glucose and plasma FFA levels. It was concluded that plasma NE concentrations may not be used as a reliable index for sympathetic activation of the liver.

The neuroendocrine hypothalamus-pituitary axis is another possible pathway by which catecholamine sensitive neurons within the hypothalamus may exert their regulatory function on peripheral glucose and FFA metabolism during exercise. Infusion of the α-adrenoceptor antagonist phentolamine into the PVN completely prevented the exercise-induced increase in plasma corticosterone concentrations, indicating that central NE activates peripheral corticosterone secretion via an α-adrenoceptor mediated mechanism in the PVN. It may be argued, however, that

this mechanism is of minor physiological importance on short term energy metabolism.

The second part of this thesis delt with some specific questions regarding the physiological significance of plasma concentrations of catecholamines and the relation between catecholamine levels in plasma and the release of energy substrates. The experiments were particularly focussed on the role of each of the two branches of the sympathoadrenal system on both the alterations in the plasma catecholamine levels as well as the energy substrate availability during exercise. Particularly the physiological relevance of the presynaptic adrenoceptor mechanisms on the nerve endings of the sympathetic nervous system was investigated. Plasma catecholamines, blood glucose, plasma FFA, and insulin concentrations were measured in exercising intact and adrenodemedullated rats, with and without administration of selective adrenoceptor agonists and antagonists. The experiments provided evidence that all physiologically active E in the blood circulation is produced by the adrenal medulla. Norepinephrine in plasma originates from the nerve endings of the sympathetic nervous system. NE of adrenal medullary origin does not contribute to plasma NE concentrations. The release of norepinephrine from the peripheral nerve endings of the sympathetic nervous systems appeared to be markedly influenced by presynaptic α- and β-adrenergic regulatory mechanisms. Stimulation of presynaptic α2-adrenoceptors reduced the outflow of neuronal NE (autoregulatory feedback control). Activation of presynaptic β2-adrenoceptors led to an enhanced release of NE. It was found that physiological quantities of blood borne E could stimulate the outflow of NE from the sympathetic nerve terminals via activation of stimulatory presynaptic β2-adrenoceptors. High levels of E caused a relative reduction in neuronal NE outflow, probably via activation of the α2-autoreceptors on the sympathetic nerve endings. Emotional stress led to very high plasma E concentrations and decreased the outflow of neuronal NE during exercise.

The distinctive catecholamine patterns were accompanied by specific alterations in the plasma concentrations of glucose, FFA, and insulin. The results indicated that both E from the adrenal medulla and NE from the peripheral nerve endings of the sympathetic nervous system play an important role in energy metabolism during exercise. The following mechanisms seemed to be involved. Epinephrine increased blood glucose levels via stimulation of α-adrenoceptor mediated glycogenolysis and gluconeogenesis in the liver. Epinephrine also reduced glucose uptake from the blood by activation of glycogenolysis in muscle, mediated by β2-adrenoceptors. Insulin release during exercise was inhibited by

E, probably via activation of α2-adrenoceptors on the pancreatic β-cell. Physiological quantities of E had no direct effect on lipolysis. Finally, E indirectly affected glucose and FFA metabolism via its β2-adrenoceptor mediated stimulatory influence on sympathetic NE release. Norepinephrine released by the peripheral sympathetic nerve endings acted in two different ways on exercise energy metabolism: as neurotransmitter in the liver and the pancreatic β-cell, and as hormone in adipose tissue. The stimulatory effect of NE on hepatic glucose production was mediated by α-adrenoceptors. Sympathetic NE had no effect on muscle glycogenolysis. Activation of the sympathetic nervous system led to inhibition of insulin release during exercise, caused by a direct effect of neuronal NE on postsynaptic α2-adrenoceptors on the pancreatic β-cell. Blood borne norepinephrine increased lipolysis via β-adrenoceptors on the fat cell.

The results of the present study indicated that the two branches of the sympathoadrenal system may be both functionally as well as metabolically dissociated. Physical activity led to the release of NE by the nerve endings of the sympathetic nervous system. Activation of the adrenal medulla was evoked by emotional stress and led to an increase in E levels in the blood. Blood glucose levels were principally influenced by adrenal E, whereas plasma FFA levels were correlated with the concentration of NE in the blood. This dissociation between sympathetic and adrenal responses is contradictory to the hitherto generally accepted view of a uniform nondiscriminating activation of the sympathoadrenal system. It means that the adrenal medulla and the sympathetic nerve endings can be activated independently of each other. It may be argued that the central nervous system can influence distinctive parts of the body via selective activation of a restricted number of pre- and postganglionic sympathetic nerves. Even an organ specific activation within the sympathetic nervous system may be suggested. An organ specific sympathetic activation in stead of a general sympathoadrenal activity can explain the controversial data concerning the role of the CNS in the regulation of plasma catecholamines and energy substrate concentrations in rest and during exercise. In particular the seemingly inconsistent changes in plasma catecholamine and energy substrate concentrations after infusion of α- and β-adrenoceptor antagonists into the hypothalamus of exercising rats in the first part of this thesis can be explained by selective activation of sympathically innervated tissues.

In summary, the data of the present study suggest that the organization of organspecific activation (or inhibition) of sympathetic output during exercise may take place at different levels. Extrahypothalamic limbic areas such as the central amygdala may serve the higher levels of organization in the central nervous response to exercise. These "central command" mechanisms may be of importance in the hypothalamic control of metabolic requirements during exercise. The present study indicates that the hypothalamus may be one of the major levels of organization in the central nervous system controlling autonomic activity. Finally, the sympathetic outflow may be affected by autonomic control mechanisms in various levels of the brain stem, at the level of the sympathetic ganglia (through peptidergic and dopaminergic modulation) and the adrenal medulla, and at the level of the peripheral sympathetic nerve terminals. The present study provides also a number of arguments for the occurrence of the last level of organization.

SAMENVATTING

Het lichaam verkrijgt zijn energie door de verbranding van allerlei energie substraten waaronder glucose en vrije vetzuren (FFA). Glucose is belangrijk omdat het door de hersenen onder vrijwel alle fysiologische omstandigheden als brandstof wordt gebruikt. Verbranding van vetzuren is voor het lichaam vooral van belang onder extreme omstandigheden zoals vasten of langdurige fysieke inspanning. Handhaving van de beschikbaarheid van glucose en FFA kan dus worden gezien als een vereiste voor het overleven van een organisme. De gehaltes van glucose en FFA in het bloed worden dan ook nauwkeurig gereguleerd. Zowel hormonale als neurale factoren spelen hierbij een rol. Hormonale factoren zijn o.a. insuline en glucagon uit de endocriene pancreas en de catecholamines adrenaline (E) en noradrenaline (NE), afkomstig uit het bijniermerg en de perifere uiteinden van het sympathisch zenuwstelsel. Tot de neurale factoren kunnen het sympathisch en het parasympathisch zenuwstelsel, en de neuroendocriene hypothalamus-hypofyse as gerekend worden.

Onder basale omstandigheden worden de glucose en FFA gehaltes in het bloed primair gecontroleerd door de perifere hormonale regulatiemechanismen, waarbij met name insuline en glucagon van belang zijn. Regulatie door het centrale zenuwstelsel (CZS) treedt pas op onder omstandigheden die afwijken van de normale rustcondities. Met name fysieke inspanning kan worden gezien als een